increase with increased cardiac output (and/or stroke volume) (3,4). Such IVUS imaging (Fig. 5A) does not correspond to the ostium, as noted in the legend, but to a more distal segment inside the wall of the aorta: an injection of saline/microbubbles in the aorta by the guiding catheter at the aortic root would have made it more obvious. The ostium in such cases is expected to be tangential, with a typical half-moon appearance on IVUS (3,4).

The aforementioned issue of hypoplasia is a fundamental one in such context, because it appears that intramural coronary arteries do not grow as normal with ageing during the first 20 years of life (this is different from the so-called Glacov phenomenon, associated with later atherosclerosis). Incidentally, our IVUS finding in similar patients carrying intussuscepted coronary arteries (currently, more than 30 cases at our institution) suggests that these coronary segments are protected both for atherosclerotic buildup and calcifications (which is quite obvious while studying older diabetic patients) (3,4).

The reported intimal thickening of 6.4 ± 5.7% of the vessel's lumen (1) may not actually be due to atherosclerosis, but to self-limited fibrous scarring related to surgery, as suggested by the fact that it does not progress with years of follow up.

We encourage Pedra et al. (1) and other investigators of such delicate subject to study all of their postoperative patients with IVUS (and not only the technically easy ones), while being aware of the afore-mentioned methodological issues. In particular, ectopic vessels with tangential origin frequently cause great difficulties of cannulation, but they are the most important cases to be studied! The issue of the normal size of a coronary artery (and of the diagnosis of hypoplasia) is a basic one. We have conceded the difficulty of such evaluation, while establishing the normal reference lumen in cases of intussuscepted coronary arteries in adults, by assuming that the distal vessel has generally normal cross section (3,4).

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REPLY

We appreciate Dr. Angelini's interest in our study (1), and we thank him for his comments. Our study was part of larger project in which left ventricular function was also evaluated late after the arterial switch operation (ASO) using rest and stress two-dimensional echocardiography. The minimum follow-up period of five years after the operation was chosen arbitrarily, and because the two-stage operation might have a deleterious impact on ventricular function, those patients managed by this approach were excluded. Although almost 300 children have been operated on for transposition of the great arteries (TGA) at our institution, only a third were candidates for the study based on the inclusion and exclusion criteria. Because of TGA the referral nature of our institution and the continental size of our country, a significant number of patients were lost to follow-up. In addition, many patients who were contacted refused to participate in the protocol because they had been doing well. This explains why only 22 patients were eventually enrolled. As such, we agree with Dr. Angelini that this may not be a representative sample of the whole series of patients. However, because the intravascular ultrasound (IVUS) findings in our study were very similar for the entire cohort (1), it is unlikely that all patients who were not enrolled had dissimilar IVUS findings.

The fact that IVUS could not be performed in two children does not mean that we only performed the technically easy cases. We simply took a safer approach; it would have been hard to justify any complications associated with technical difficulties in a symptom-free population, especially considering that the use of IVUS for coronary assessment late after the ASO for TGA is a delicate subject, as Dr. Angelini correctly pointed out in his letter.

Although the arguments presented by Dr. Angelini were very interesting, we disagree that our Figure 5A (1) represents an intramural coronary segment. Indeed, an intramural coronary artery may be occasionally found in neonates with TGA, posing technical difficulties to transfer the aortocoronary flap to the neoaorta and increasing the surgical risks (2). However, none of the patients in our series had this anatomical pattern at the operation. In addition, real-time cross-sectional IVUS imaging in that patient did not show any phasic compression or a half-moon appearance of the ostium. In fact, the ostium possessed an elliptical configuration, which had a cross-sectional area very similar to the adjacent distal coronary segment.

Acquired compression, torsion, and stretching of the proximal coronary arteries certainly occur after the ASO. In fact, these lesions are associated with early coronary events after a technically difficult operation, as shown by Legendre et al. (3). Late coronary events, albeit uncommon, are unlikely to be explained on the same grounds. In their series, Legendre et al. (3) reported a patient who had a normal coronary angiogram and eventually developed a late coronary artery obstruction, indicating that there are other mechanisms involved in late obstructions. The observation that most of the studied vessels in our series had proximal eccentric intimal thickening suggests the development of early atherosclerosis in the reimplanted coronary arteries (1), which may have a role in the genesis of late coronary events. Severe intracoronary fibrous proliferation may occur after the ASO, resulting in infarction and death (4).

At the moment, no matter what mechanism is involved, there is not enough evidence to state that these abnormalities are self-limited and do not progress with time. In fact, we would rather take a more cautious approach, highlighting the need to develop strategies to control risk factors for coronary artery disease in the late follow-up of these patients.

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Microvolt T-Wave Alternans: Where Do We Go From Here?

The recent meta-analysis by Gehi et al. (1) assessed the value of microvolt T-wave alternans (MTWA) testing to predict cardiac arrhythmic events in differing patient populations. Their analyses provide a summary estimate of the predictive value of MTWA in patients with ischemic and non-ischemic cardiomyopathy. In their discussion, the investigators point out that while MTWA has shown promise in identifying high-risk patients, studies have been hampered by small sample sizes. Importantly, this has limited the comparisons of baseline characteristics between individuals with negative and non-negative MTWA tests in most studies and has prevented adequate multivariable adjustment for potential confounders.

This raises questions as to whether MTWA is simply a surrogate marker of patients with greater disease burden and severity. If so, differences in age, left ventricular ejection fraction (LVEF), clinical comorbidities, and medication treatment between individuals with negative and non-negative MTWA tests may explain its predictive power. We believe that in order for MTWA to gain wider acceptance as a risk stratification tool, three types of analyses are needed. First, multivariable modeling that adjusts for demographics, LVEF, clinical comorbidities, medication treatment, as well as electrophysiologic variables (e.g., Holter monitoring, QRS duration, electrophysiologic study) should be done to show that MTWA is an *independent* predictor of cardiac arrhythmias. Gehi et al. (1) themselves acknowledge that MTWA does not offer incremental prognostic utility unless it can be shown to add predictive power beyond known risk factors for cardiac arrhythmia (such as LVEF in patients with ischemic cardiomyopathy).

Second, studies of MTWA should provide analyses of all-cause mortality in addition to arrhythmic mortality. Prior studies of MTWA that used a primary end point of cardiac arrhythmic events may be limited as they did not consider competing risks whereby MTWA may predict arrhythmic, but not all-cause, mortality.

Finally, even if future studies demonstrate that MTWA offers incremental prognostic utility in assessing high-risk patients, its true utility for risk stratification will only be known when the mortality reduction benefit of implantable cardioverter-defibrillators (ICDs) is evaluated in patients who test MTWA-negative and non-negative. This could be accomplished by randomizing patients to ICD therapy after MTWA testing, but such a clinical trial might raise ethical concerns given that some high-risk patients may be denied life-saving therapy. To justify such a clinical trial, additional cohort analysis using propensity scores for ICD therapy based on MTWA status may be needed (2).

Gehi et al. (1) are to be commended for their synthesis of a large pool of clinical data on MTWA. Future studies of MTWA should focus on its incremental prognostic utility after multivariable adjustment, but ultimately the true utility of MTWA in risk-stratifying high-risk patients will remain uncertain unless it can be shown that the benefit of ICDs differs by MTWA subgroup.

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REPLY

We appreciate the thoughtful comments of Dr. Chan and colleagues regarding our meta-analysis of microvolt T-wave alternans (MTWA) and wish to expand upon several points (1).

As dicussed by Dr. Chan and colleagues and as we pointed out in our Discussion section, very few studies have demonstrated whether MTWA is predictive of future arrhythmic events independent of other well-established clinical predictors. There is substantial evidence regarding the prognostic utility of other risk predictors, including ejection fraction (EF), signal-averaged electrocardiogram (ECG), heart rate variability, electrophysiologic study, and baroreflex sensitivity. Though MTWA may be the test currently in vogue, until MTWA is shown to add substantial